IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: WALLACH=27A

In re Application of:	)	Conf. No.: 3756
	)	
David WALLACH et al.	)	Art Unit: 1633
	)	
Appln. No.: 10/761,370	)	Examiner: I. Popa
	)	
Filed: January 22, 2004	)	Washington, D.C.
	)	
For: MODULATORS OF THE FUNCTION OF RECEPTORS OF THE TNF/NGF RECEPTOR	)	December 28, 2009

REPLY BRIEF

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, Mail Stop Appeal Brief - Patents
401 Dulany Street
Alexandria, VA 22314

Sir:

The present reply brief is responsive to the Examiner's Answer of October 28, 2009, and is in full compliance with 37 CFR §41.41.

The Examiner Incorrectly States That the Present Claims Encompass Polyclonal Antibodies Raised Against Fip-2

In the examiner's arguments in response to appellants' main brief in this case as it relates to claim 1, the examiner states at page 15 of the Examiner's Answer:

> In response to this argument, it is noted that claim 1 broadly encompasses any antibody type, including polyclonal antibodies. A polyclonal anti-Fip-2 antibody preparation is a mixture of antibodies; because of sequence homology between the C-terminal of FIP-2 and RAP-2, this polyclonal antibody preparation necessarily comprises antibodies which also recognize RAP-2 (i.e., the genus necessarily comprises the subgenus). The argument that the subgenus does not represent the majority of the genus is irrelevant because the claims do not require that the antibodies specific for RAP-2 (i.e., the subgenus) be isolated from the polyclonal preparation (i.e., the genus). With respect to Appellant's citation from MPEP 2144.08, such is applicable when the prior art does not specifically discloses [sic] the claimed species. In the instant case, since the genus necessarily comprises the subgenus, there is no need to specifically select the subgenus.

Apparently the examiner's position is that the present claims read on a polyclonal antibody preparation made using FIP-2 as an immunogen. This interpretation of claim 1 is incorrect.

Claim 1 includes the language, "A molecule comprising an antibody **specific for** a RAP-2 … protein …." The term "specific for" cannot be read out of the claim. It is true that claim 1 reads on polyclonal antibodies, but a polyclonal antibody specific for FIP-2 is not a polyclonal antibody specific for RAP-2. A polyclonal antibody raised against FIP-2 (i.e., specific for FIP-2), will have very

little, if any, binding capability to RAP-2. Thus, it does not fall within the scope of claim 1. On the other hand, a polyclonal antibody specific for RAP-2, i.e., raised against RAP-2, will have preferential binding for RAP-2 as compared to any other protein, and thus falls within the scope of claim 1.

Paragraph [0180] of the present specification defines the term "antibody" so as to include "polyclonal antibodies." The term "polyclonal antibodies" is defined in paragraph [0181] of the present specification where it states:

> Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen.

Paragraph [0166] states:

> As noted above, the RAP-2 protein, or its analogs, fragments or derivatives thereof, of the invention may also be used as immunogens (antigens) to produce **specific** antibodies thereto. These antibodies may also be used for the purposes of purification of the RAP-2 protein (e.g., RAP-2 or any of its isoforms) either from cell extracts or from transformed cell lines producing RAP-2 protein, or its analogs or fragments.

The same paragraph goes on to state that such antibodies specific for RAP-2 may be used as an important diagnostic tool.

Paragraph [0168] states:

> As set forth hereinabove, the RAP-2 protein may be used to generate antibodies **specific** to RAP-2 proteins, e.g., RAP-2

> and its isoforms. These antibodies or fragments thereof may be used as set forth hereinbelow in detail, it being understood that in these applications the antibodies or fragments thereof are those **specific** to RAP-2 proteins.

While it is true that during patent examination the pending claims must be given their broadest reasonable interpretation consistent with the specification (see MPEP 2111), this section of the MPEP also states that the broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. Thus, according to the above-quoted portions of the specification, those of ordinary skill in the art would understand that the antibodies must have that amount of specificity that is obtained when raising antibodies using RAP-2 as an immunogen (antigen). At the very least, this means that the antibodies, whether polyclonal or monoclonal, must have preferential binding to RAP-2.

The polyclonal antibodies that would be obtained when using FIP-2 as an immunogen, would not be "specific for" RAP-2 as they would preferentially bind to FIP-2 and only incidentally bind to RAP-2 (if at all) because only a small percentage of those antibodies (if any) would have the property of binding to RAP-2.

Accordingly, the polyclonal antibody that the examiner says is made obvious by the combination of references

does not fall within the scope of claim 1 as that polyclonal antibody is not "specific for" RAP-2 protein.

The Examiner Is Incorrect In Stating That There Is No Showing Of Improved Properties In The Instant Case

At page 16 of the Examiner's Answer, the examiner states:

> In the instant case, there is no showing of any improved property (it is noted that the specification only provides hypothetical examples of obtaining polyclonal and monoclonal antibodies; the specification does not provide any example of polyclonal or monoclonal antibody directed to RAP-2 which would exhibit unexpectedly improved properties). Furthermore, the property of binding RAP-2 is inherent to the polyclonal anti-Fip-2 antibody preparation taught by the prior art, i.e., the property is present in the prior art.

The present rejection is not an anticipation rejection. It is an obviousness rejection. Any time an obviousness rejection is made, a *prima facie* case of obviousness can be rebutted by a showing of unexpected results. The examiner has conceded that nobody has ever made antibodies to FIP-2 in the prior art. If the Board accepts the examiner's argument that a polyclonal antibody raised against FIP-2 would fall within the scope of claim 1 (notwithstanding applicant's position to the contrary stated above) and thus would be *prima facie* obvious, such a

polyclonal antibody would have unexpected properties that rebut such a *prima facie* case of obviousness.

No one of ordinary skill in the art reading the references of record[1] would expect that the anti-FIP-2 polyclonal antibodies would be specific for RAP-2 (assuming that applicants proposed definition of "specific for" is not accepted by the Board). Specificity for RAP-2 is a property that by definition is carried by the antibodies of the present claims and would not be obvious from the prior art. The examiner states that this property would be **inherent** in the antibodies of the prior art. However, there are no "antibodies of the prior art," i.e., the prior art references do not disclose anti-FIP-2 antibodies. There is no anticipation rejection. The fact that a result might be inherent in following the combined teachings of the prior art is quite immaterial if one of ordinary skill in the art would not appreciate or recognize that inherent result. As the CCPA pointed out in *In re Spormann*, 363 F.2d 444, 150 USPQ 449, 452 (CCPA 1966):

> The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is

[1] It is noted that both the examiner and applicant have referred to the references as "Yongan." In fact, the name of the author is Yongan Li. Yongan is his given name and Li is his family name. Indeed, he is a co-inventor of the present invention. Thus, the references should more properly be referred to Li et al. or the Li thesis.

> not necessary known. Obviousness cannot be predicated on what is unknown.

Accordingly, if, nothwithstanding appellant's position that the examiner has not established a *prima facie* case of obviousness because polyclonal antibodies specific for FIP-2 do not fall within the scope of a claim requiring an antibody specific for RAP-2, the Board finds that a *prima facie* case of obviousness has been established, such *prima facie* obviousness is rebutted by the unexpected property that antibodies against FIP-2 can also bind to RAP-2. RAP-2 is a novel protein that was not known to the prior art. The ability to bind to RAP-2 is a significant and important property of the antibodies of the present invention. The above-quoted portions of the present specification show that appellants were in possession of antibodies with this property. The examiner's criticism of the specification is irrelevant as there is no 35 USC 112 rejection of record in this case. For this reason as well, the rejection of claim 1 and those claims dependent there from must be reversed.

The Examiner Provides No Support For Her Statement That At least One Of The Epitopes Of FIP-2 Would Be Able to Elicit An Antibody Response

At page 17 of the Examiner's Answer, the examiner concedes that the only area of sequence identity of greater than 5 amino acids between RAP-2 and FIP-2 is the eight amino

acid region from amino acid 566 to 573 of FIP-2. However, the examiner goes on state:

> While this is true, it is noted that the C-terminal domains of RAP-2 and Fip-2 are approximately 57% homologous and comprise several identical stretches of 4-5 amino acids in length, which constitute epitopes for eliciting immune responses (see Fig. 3B).

The examiner cites no reference which would support a contention that a region in two different molecules that is 57% homologous must include epitopes for eliciting immune responses. It is the examiner's burden to establish inherency, not applicants. Until the examiner submits sufficient evidence to satisfy the examiner's burden, there is no reason for applicant to come in with evidence of his own to rebut it.

At page 18 of the Examiner's Answer, the examiner states:

> [T]he C-terminal domain of Fip-2 shares many epitopes with the C-terminal domain of Rap2; for certain, at least one of these epitopes would be able to elicit an antibody response.

The examiner cites no support for this alleged certainty. In the entire region of what the examiner considers to be 57% homology, there is only one region with eight identical amino acids between the two proteins and there are only two other regions with five identical amino acids. The examiner has

given no explanation of why any of these three regions would be expected to be immunodominant so as to raise antibodies against FIP-2 that will also bind to RAP-2. Without such evidence, the examiner has not supported her burden, particularly since there are many reasons to be believe that this would not necessarily happen, given the unpredictability in this field. These have been discussed in detail in appellant's main brief and need not be repeated here.

The Examiner Presents No Convincing Reasons and No Rebuttal Of Appellant's Arguments Regarding Claims 17 and 18

At pages 18 and 19 of the Examiner's Answer, the examiner states that the claims do not require selection by binding to RAP-2 and a selection step by binding to RAP-2 is not necessary because a monoclonal antibody directed against the common epitopes would necessarily bind RAP-2.

All of the examiner's previous arguments about polyclonal antibodies falling within the scope of the claims so that it is not necessary to find a claimed sub-genus, are irrelevant when considering claims 17 and 18. Claims 17 and 18 are clearly directed to specific species of monoclonal antibodies that are specific for RAP-2. The prior art teaches no monoclonal antibodies specific for FIP-2, but the examiner states that the prior art makes it obvious to raise monoclonal antibodies against FIP-2 and that a monoclonal antibody that

happens to be directed to a sequence of FIP-2 which also appears in RAP-2 would **inherently** meet the requirements of claim 17.

However, if anything, the prior art suggests a genus of monoclonal antibodies that are specific for FIP-2. This entire genus is clearly not read on by claim 1. Only specific antibodies (even assuming that such specific antibodies exist) will fall within the scope of claim 1. These are specific **species** of antibody. The fact that the genus of monoclonal antibodies may be *prima facie* obvious does not automatically mean that every species within this genus is also obvious, as discussed in appellant's main brief. Those particular species that fall with the scope of claim 17 all have unexpected properties. Those of ordinary skill in the art would expect that they would bind to FIP-2 (as will all the other species of the genus). The certain limited number of species (if any) that bind to the novel RAP-2 protein have the totally unexpected property of binding to RAP-2, which permits an important and unexpected utility, such as for isolating RAP-2 from a mixture of RAP-2 and other proteins.

Appellant has never suggested that the claims require selection steps. The claims are product claims and have no product-by-process limitations. The reference to selection in appellant's argument was only used to assist in

the understanding of appellant's point. The fact is that of the myriads of antibodies that can be raised against FIP-2, only a very small number (if any) will have the properties required by claim 17 (i.e, be specific for RAP-2). That species of monoclonal antibody has unexpected properties in that no one of ordinary skill in the art reading the prior art would realize that individual ones of the myriad of monoclonal antibodies against FIP-2 might have the additional property of binding to RAP-2. This species of antibody is not made obvious by references, which do not recognize the existence of RAP-2 (which is novel). The examiner has provided no reason to identify only the specific species of anti-FIP-2 monoclonal antibodies that happen to also have the unexpected property of binding to the novel RAP-2 protein. Without being directed in some way to that particular species from among the myriad species of the genus that is allegedly made *prima facie* obvious, a claim directed only to that species cannot be obvious.

Accordingly, claim 17 and 18, both of which clearly require individual species (or a sub-genus) within the genus which would allegedly be *prima facie* obvious from the prior art, would not themselves be obvious for the reasons provided.

CONCLUSION

For all of the reasons presented herein, in conjunction with the reasons explained in appellant's main brief, reversal of the examiner and withdrawal of the 35 USC 103 rejection of claims 1 and 17-19, and particularly with respect to claims 17 and 18, are therefore earnestly solicited.

Respectfully submitted,

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